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Percutaneous Mitral Repair With the MitraClip System

Safety and Midterm Durability in the Initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Cohort

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Objectives We undertook a prospective multicenter single-arm study to evaluate the feasibility, safety, and efficacy of the MitraClip system (Evalve Inc., Menlo Park, California).

Background Mitral valve repair for mitral regurgitation (MR) has been performed by the use of a surgically created double orifice. Percutaneous repair based on this surgical approach has been developed by use of the Evalve MitraClip device to secure the mitral leaflets.

Methods Patients with 3 to 4+ MR were selected in accordance with the American Heart Association/American College of Cardiology guidelines for intervention and a core echocardiographic laboratory.

Results A total of 107 patients were treated. Ten (9%) had a major adverse event, including 1 nonprocedural death. Freedom from clip embolization was 100%. Partial clip detachment occurred in 10 (9%) patients. Overall, 79 of 107 (74%) patients achieved acute procedural success, and 51 (64%) were discharged with MR of ≤1+. Thirty-two patients (30%) had mitral valve surgery during the 3.2 years after clip procedures. When repair was planned, 84% (21 of 25) were successful. Thus, surgical options were preserved. A total of 50 of 76 (66%) successfully treated patients were free from death, mitral valve surgery, or MR >2+ at 12 months (primary efficacy end point). Kaplan-Meier freedom from death was 95.9%, 94.0%, and 90.1%, and Kaplan-Meier freedom from surgery was 88.5%, 83.2%, and 76.3% at 1, 2, and 3 years, respectively. The 23 patients with functional MR had similar acute results and durability.

Conclusions Percutaneous repair with the MitraClip system can be accomplished with low rates of morbidity and mortality and with acute MR reduction to < 2+ in the majority of patients, and with sustained freedom from death, surgery, or recurrent MR in a substantial proportion (EVEREST I; NCT00209339. EVEREST II; NCT00209274). (J Am Coll Cardiol 2009;54:686–94) © 2009 by the American College of Cardiology Foundation

Mitral valve (MV) repair with the use of a surgical approach to create a double-orifice valve was first performed by Alfieri in 1991 (Fig. 1) (1–3). Durable results in surgically-treated patients without annuloplasty have been described in selected patients for as long as 12 years after surgical repair (4,5). Percutaneous mitral repair based on this surgical technique has been developed by the use of a clip rather than suture to secure the mitral leaflets (6,7). The MitraClip

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device (Evalve, Inc., Menlo Park, California) is delivered to the MV via percutaneous femoral venous transseptal access. The clip is aligned above the MV and advanced across the mitral orifice before grasping and coapting the leaflets. Six-month results of percutaneous mitral repair for mitral regurgitation (MR) by use of the MitraClip system was previously reported in a cohort of 55 patients (8). This report details clinical results in a cohort of the first 107 patients followed for as long as 3 years. This therapy uses a first-in-class catheter-based percutaneous device for the treatment of degenerative and functional MR, and results, including all patients at 12 months and a number of patients with more than 1-year follow-up, are reported.

Methods

Study design. This is a prospective, multicenter, single-arm study. The objective was to evaluate the feasibility, safety, and efficacy of the MitraClip device. The study was approved by the Food and Drug Administration, Health Canada, and all of the participating local institutional review boards and Canadian ethics boards. All patients gave informed written consent. All echocardiograms were reviewed by a core laboratory.

Study sites were selected for expertise in both catheter approaches to valvular heart disease and with surgical repair. Interventional operators all had experience with transseptal puncture. Ninety percent of sites (28 of 31) have a surgeon investigator who performed ≥25 MV surgeries yearly. Thirty-one North American sites enrolled 107 patients, and 70% of procedures represent first, second, or third procedures at a site (Online Appendix).

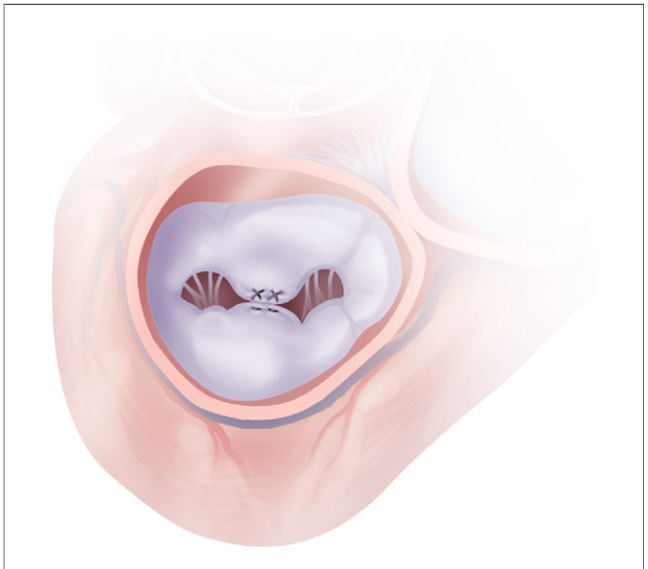

Figure 1 Double Orifice Surgical MV Repair With Suture

Illustration depicts a double-orifice mitral valve (MV) surgical repair. The MV is viewed from the left atrial side. The middle scallops of the anterior and posterior leaflets have been sutured together, which creates a double orifice, edge-to-edge, or bow-tie repair.

Study population. The study includes 55 patients treated in the EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Phase I feasibility trial, and 52 roll-in patients treated in the EVEREST II pivotal trial, who represent the pre-randomization start-up experience.

Abbreviations and Acronyms

ACC = American College of Cardiology
AHA = American Heart Association
APS = acute procedural success
ASE = American Society of Echocardiography
CDS = Clip Delivery System
LV = left ventricle
MAE = major adverse event
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
STS = Society of Thoracic Surgeons

MitraClip system. The MitraClip system uses a tri-axial catheter system with an implantable clip. The Guide Catheter is 24-F proximally, 22-F at the atrial septum, and is delivered with a tapered dilator. A dial on the proximal end of the guide catheter allows deflection of the distal tip. The Clip Delivery System (CDS) has the MitraClip attached to its distal end. This system uses 2 dials that permit medial-lateral and anteroposterior steering. The MitraClip device (Fig. 2) is a 4-mm wide cobalt/chromium implant with 2 arms, which are opened and closed by a mechanism on the CDS handle. On the inner portion of the clip are 2 "grippers" adjacent to each arm to secure the leaflets as they are "captured" during closure of the arms. Each leaflet is independently secured between an arm and a gripper. The clip has a locking mechanism to maintain closure. The clip arms and grippers are covered with polyester fabric to promote tissue ingrowth.

Procedural technique. The procedure is performed, with the patient under general anesthesia, with the use of fluoroscopy and transesophageal and, on occasion, transthoracic, echocardiographic guidance. After transseptal puncture, heparin is administered. The transseptal sheath is exchanged for the steerable guide catheter and dilator. The CDS is introduced into the guide catheter, and the MitraClip device is advanced into the left atrium. By the use of echocardiographic and fluoroscopic guidance, the clip is steered until axially aligned and centered over the origin of the regurgitant jet. The clip is opened to extend the 2 arms and advanced into the left ventricle (LV) below the mitral leaflets. The clip is retracted until both leaflets are grasped and then closed to coapt the mitral leaflets. Leaflet insertion into the clip and MR reduction are assessed by the use of 2-dimensional and Doppler echocardiography. If necessary, the clip can be reopened and the leaflets released and then repositioned. If the clip must be withdrawn into the left atrium, the arms may be inverted in the ventricle, providing a smooth profile for retraction to prevent entangling the chordae tendinea. After adequate reduction of MR has been achieved under hemodynamic challenge, the clip is deployed, and the CDS and guide catheter are withdrawn.

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Figure 2 The MitraClip Device

The device is covered with polyester fabric to facilitate tissue in-growth. The distal gripping element helps with leaflet fixation. The clip delivery system exits through a guide catheter.

After the first 10 patients were enrolled, the protocol was revised to allow a second clip placement if needed. Repeat hemodynamic and echocardiographic assessments were performed after clip placement. Patients were treated with aspirin 325 mg daily for 6 months and clopidogrel 75 mg daily for 30 days.

Patient selection. Patients were selected if they met class I indications for intervention from the 1998/2006 American College of Cardiology (ACC)/American Heart Association (AHA) Joint Task Force recommendations regarding therapy for valvular heart disease (9,10). Patients with moderate-to-severe (3+) or severe (4+) functional or degenerative MR with symptoms, or if asymptomatic, with compromised LV function (ejection fraction <60% or end-systolic dimension >45 mm) were candidates (Table 1). All echocardiograms were assessed by an independent core echocardiographic laboratory (University of California at San Francisco, San Francisco, California). Mitral regurgitation was graded according to the criteria of the American Society of Echocardiography (ASE) guidelines by the use of quantitative (regurgitant volume, regurgitant fraction) and qualitative (color Doppler and pulmonary venous flow) criteria (11,12). To be included, moderate-to-severe (3+) or severe (4+) MR by use of the integrative approach per the ASE guidelines (Table 2) was required. Key anatomic inclusion criteria included a regurgitant jet origin associated with the A2 to P2 segments of the mitral valve and, for patients with functional MR, a coaptation length of at least 2 mm, a coaptation depth of no more than 11 mm, and for patients with leaflet flail, a flail gap <10 mm and a flail width <15 mm (Fig. 3). All patients were candidates for MV surgery, in the event surgery was required for potential complications. Major exclusions are shown in Table 1.

Data analysis. The data from all 107 patients were analyzed per the EVEREST II protocol definitions and prespecified end points. Patients who did not receive a clip or underwent MV surgery after the clip implant did not have further follow-up during the first part of the study (8). Primary end points were analyzed for the per-protocol population, defined as patients receiving a clip implant with reduction of MR to ≤2+, also referred to as acute procedural success (APS). The composite primary safety end point was major adverse events (MAEs) at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for adverse events, renal failure, transfusion of >2 U of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for >48 h, deep wound infection, septicemia, and new onset of permanent atrial fibrillation (determined at 12 months). The composite primary efficacy end point was freedom from MR >2+, freedom from cardiac surgery for valve dysfunction, and freedom from death at 12 months.

Echocardiograms were performed by the use of a prespecified protocol at baseline; pre-discharge; at 1, 6, 12, 18, and 24 months; and yearly up to 5 years. The 12-month follow-up MR reduction goal was defined as MR severity of ≤2+, based on the ACC/AHA guidelines (9,10). The goal in the cardiac catheterization laboratory was to reduce MR to mild (1+) or less with optimal placement of the MitraClip device. An overall MR grade was assigned by use of the integrative method defined by the ASE guidelines (11,12). Vena contracta width and regurgitant orifice area were recorded but not included as parameters for MR assessment because they have not been validated for a double orifice valve. To evaluate for the potential development of MV stenosis, MV area measured by planimetry, pressure half-time, and peak and mean gradients were assessed. After percutaneous mitral repair, each of the 2 orifices was planimetered at the level of the clip and summed to determine valve area.

Table 1 Key Eligibility Criteria and Key Exclusion Criteria

Key inclusion criteria
Candidate for mitral valve repair or replacement surgery
Moderate to severe (3+) or severe (4+) chronic mitral valve regurgitation and symptomatic with LVEF >25% and LVID-s ≤55 mm or asymptomatic with 1 or more of the following:
LVEF >25% to 60%
LVID-s ≥40 to 55 mm
New onset of atrial fibrillation
Pulmonary hypertension defined as pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise.
Key exclusion criteria
Recent myocardial infarction
Any interventional or surgical procedure within 30 days of the index procedure
Mitral valve orifice area <4 cm^2
Renal insufficiency, endocarditis, rheumatic heart disease
Previous mediastinal surgery in the first 27 patients

LVEF = left ventricular ejection fraction; LVID-s = left ventricular internal diameter-systole.

Table 2 Mitral Regurgitation Grade Criteria*

Variable	Mild 1+	Moderate 2+	Moderate to Severe 3+	Severe 4+
Color flow Doppler	Small Central <4 cm^2 or <10% of LA area	Moderate Central 4–6 cm^2 or 10% to 30% of LA area	Large Central 6 to <8 cm^2 or 30% to <40% of LA area or eccentric to first PV	Large Central ≥8 cm^2 or ≥40% of LA area or eccentric to second PV
Pulmonary vein flow	Systolic dominant	Diastolic dominant	All diastolic	Systolic reversal
Regurgitant volume (ml/beat)	<30	30–44	45–59	≥60
Regurgitant fraction (%)	<30	30–39	40–49	≥50

*Based on the American Society of Echocardiography published guidelines for the quantitation of native valvular regurgitation, which have not previously been applied in a therapeutic trial (11,12). LA = left atrium; PV = pulmonary vein.

Results

One hundred seven patients were treated, including patients (79%) with degenerative or combined degenerative and functional disease and 23 patients (21%) with pure functional MR. Clinical features are shown in Table 3. The median age was 71 years (range 26 to 88 years), and 62% of patients were older than 65 years of age. Among patients with functional MR, there was a history of coronary artery disease in 74% and previous bypass surgery in 43%.

One clip was placed in 65 patients (61%), 2 clips in 31 patients (29%), and no clips in 11 patients (10%; inability to reduce MR in 8 patients [7%] and transseptal complications in 3 patients [3%]). Two patients underwent reintervention to have a second clip placed. There was a steep procedural learning curve, with rapid reduction in the procedure and device times throughout the study. For all patients, including those who did not receive a clip, overall procedure time, defined as the time from transseptal access with the guide

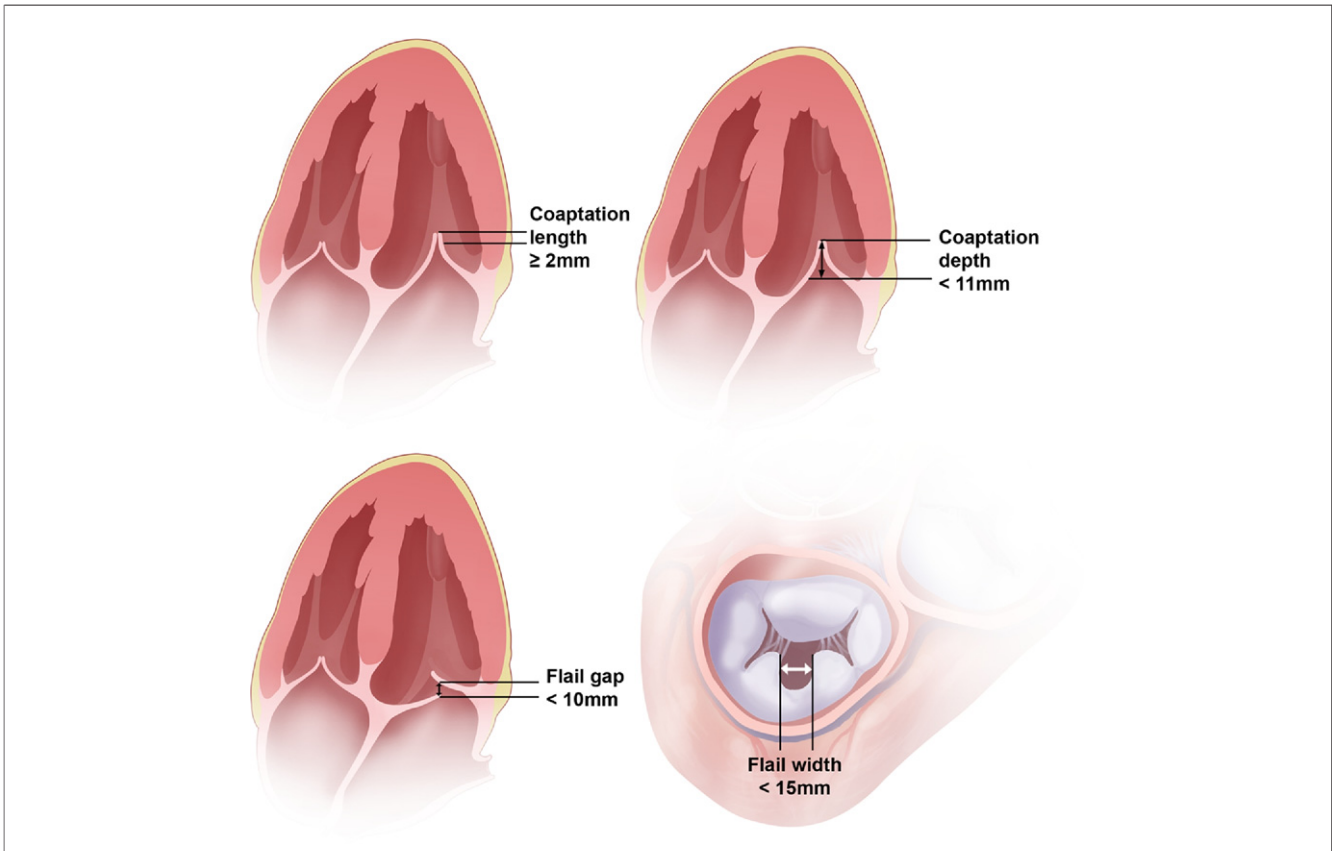

Figure 3 Key Anatomic Eligibility Criteria

The coaptation length must be at least 2 mm. Coaptation depth must be <11 mm. If a flail leaflet exists, the flail gap must be ≤10 mm, and the flail width must be ≤15 mm. These anatomic characteristics are necessary for sufficient leaflet tissue for mechanical coaptation when the MitraClip device is used.

Table 3 Baseline Demographics and Clinical Features

	Baseline (n = 107)
Median age (yrs), median (range)	71 (26–88)
Age >65 yrs, %	62
Male sex, %	62
Diabetes mellitus, %	21
Hypertension, %	69
Chronic obstructive pulmonary disease, %	12
History of congestive heart failure, %	53
History of coronary artery disease, %	36
Previous coronary artery bypass graft, %	20
Atrial fibrillation, %	29
Ejection fraction, % (median)	62
New York Heart Association functional class III or IV, %	46

catheter to guide removal from the vein, was 231 min. Device time, defined as time from guide catheter insertion to CDS retraction into the guide catheter, was 175 min. Although 93% of patients were among the first 3 procedures at a given site, the overall procedure time decreased to 181 min, with 146 min of device time in the last 30 patients of this cohort. Currently procedures are frequently completed with a device time of approximately 90 min.

In-hospital outcomes are shown in Table 4. There was no procedural mortality. Ten patients experienced an MAE at 30 days, resulting in a composite primary safety end point of 9.1% (95% confidence interval: 5.1% to 16.3%) by intention to treat, including a single death in an 81-year-old patient with a Society of Thoracic Surgeons (STS) operative mortality risk score of 18.3% in whom no clip was placed and MR was not reduced. One patient with a history of transient ischemic attack had a nonembolic stroke with a neurological deficit lasting >72 h, which resolved within 30 days. Nonelective cardiac surgery was performed in 2 patients for transseptal complications. Bleeding requiring transfusion ≥2 U occurred in 4 patients. One patient underwent reoperation for failed surgical mitral valve repair 19 days after valve repair after an unsuccessful MitraClip procedure, and 1 patient required ventilation for >498 h.

Of the 10 patients meeting the MAE safety end point, close to one-half received transfusions of ≥2 U of blood.

Table 4 In-Hospital Outcomes

In-Hospital Outcomes*	Incidence (n = 107)
Death unrelated to MitraClip device	1 (0.9)†
Mechanical ventilation >48 h	2 (1.8)†‡
Bleeding requiring transfusion ≥2 U (procedural)	4 (3.7)‡
Bleeding requiring transfusion ≥2 U (post-MV surgery)	1 (0.9)
Transseptal complications	3 (2.8)‡
Renal failure or dialysis	0 (0)
Length of hospital stay, days	3.2 ± 3.9
Discharge home (without home health care)	104 (98)

Values are n (%) or mean ± SD. *Includes patients that went to surgery after clip procedure (n = 10). †One patient on ventilation subsequently died. ‡One patient experienced a transseptal complication leading to mechanical ventilation >48 h and bleeding requiring transfusion ≥2 U. MV = mitral valve.

In-hospital mortality was <1%. Mitral valve area (planimetry) was 5.7 ± 1.5 cm^2 (n = 94) at baseline, 3.2 ± 1.2 cm^2 (n = 73) at discharge, and 3.5 ± 1.1 cm^2 (n = 62) at 12 months. The sample size decreased as the result of some crossover to surgery and patients with incomplete measurements of the dual orifices after clip placement. The smallest mitral valve area by planimetry was 1.9 cm^2, and clinically significant stenosis was defined as <1.5 cm^2 per the protocol.

No clip embolization has occurred at any time point. Partial clip detachment, defined as detachment of a single leaflet from the clip, occurred in 10 patients (9%). Partial clip detachment occurred in 3 patients during the procedure, in 1 before hospital discharge, and in 5 patients between discharge and 30 days. Only 1 partial clip detachment occurred after 30 days; MR recurrence without detachment was noted on the 6-month echocardiogram and worsening of MR, and partial clip detachments were detected on the 12-month echocardiogram. None of the partial clip detachments were associated with urgent intervention and, in all but 1 patient who had recurrent symptoms, these events were detected on protocol-driven echocardiography.

Overall APS was achieved in 79 of 107, or 74% of patients. The flow chart (Fig. 4) shows the outcomes among patients both with and without clip implantation and with and without APS. Of the 79 patients with APS, 64% were discharged with mild MR (1+) and 13% had MR graded as mild to moderate (1 to 2+). Thus, 77% had <2+ MR. At 12 months, not including crossover to surgery, 50 of 76 patients (66%) had echocardiographic follow-up and continued with MR ≤2+. Three patients did not have an echocardiogram performed at 12 months. Fifteen patients experienced recurrent MR >2+ and have not undergone MV surgery. Of these 15 patients, 3 patients experienced a 1-grade MR reduction with improved symptoms, and 12 patients continued with no MR reduction from baseline. Of

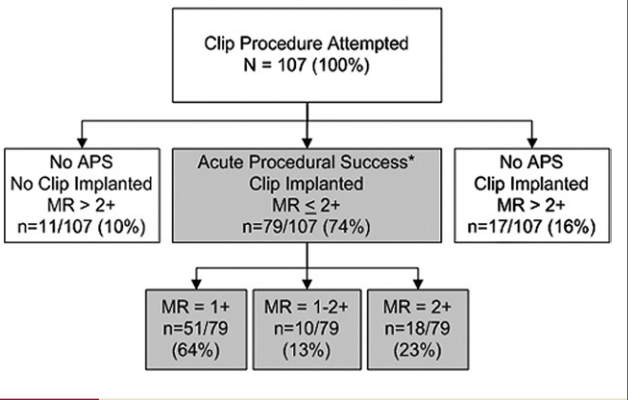

Figure 4 Efficacy Results Through Discharge

This chart shows the flow of patients from the point of clip procedure attempt through hospital discharge. *Acute procedural success (APS) is defined as placement of 1 or more clips resulting in a discharge mitral regurgitation (MR) severity of ≤2+, as determined by the Core Laboratory.

the remaining 11 APS patients, 9 experienced recurrent MR and underwent MV surgery during the first year of follow-up, 1 of whom died after surgery, 1 with ongoing MR ≤2+ died in the first year, unrelated to the clip, and 1 patient with 3+ MR at 6 months died of cardiac arrest before 12 month follow-up. As previously reported, no mitral stenosis occurred (13).

Of the 106 patients who were discharged from the hospital, 104 (98%) were discharged to home with self care, whereas the remaining 2 patients in whom MR was not reduced sufficiently with the clip underwent MV surgery during the index hospitalization and were discharged to a cardiac rehabilitation facility.

On an intent-to-treat basis, 96 (90%) of 107 patients successfully achieved a reduction in MR from either the clip or subsequent MV surgery after attempted clip. Of the remaining 11 patients who did not achieve MR reduction to ≤2+ after the clip, 10 patients did not undergo MV surgery after unsuccessful clip attempt, and 1 patient underwent MV replacement surgery 19 days after failed MV repair surgery. Seventy percent (75 of 107) of patients remained surgery free after a median follow-up of 680 days. The remaining 32 patients underwent MV surgery after a clip procedure. Twenty-three patients had MV surgery after clip implantation, and 9 patients had surgery after no clip was implanted. Surgery was performed 14 ± 21 days after the procedure in cases where no clip was implanted and 234 ± 319 days after surgery in cases in which a clip had been placed ($p = 0.003$).

The pre-operative strategy was known for 31 of 32 patients who underwent surgery after a clip procedure. In these 31 patients, 87% of surgeries (27 of 31) were performed as planned pre-operatively, whereas 13% (4 of 31) of patients had replacement after attempted repair (3 repairs converted to replacement intraoperatively, 1 patient underwent MV replacement 19 days after failed MV repair) (Fig. 5) (14). When repair was planned after a clip procedure, 84% (21 of 25) were successfully repaired. When MV replacement was performed, the majority (60%, 6 of 10) of replacements were planned because of complex disease, advanced age, and/or comorbidities. One additional replacement occurred without a known pre-operative strategy. Successful surgical repair with clip removal was performed up to 18 months after percutaneous mitral repair. In summary, surgical options were preserved.

The composite primary efficacy end point (freedom from MR >2+, freedom from cardiac surgery for valve dysfunction, and freedom from death for the per-protocol population at 12 months) was 66% (95% confidence interval: 55% to 75%). Of the 65 patients with matched New York Heart Association (NYHA) functional class data at baseline and 12 months, baseline NYHA functional class was I/II in 29 patients (45%) and III/IV in 36 patients (55%). At 12 months, 60 patients (92%) were NYHA functional class I/II, and 5 patients (8%) were III/IV. Clinical symptoms were improved in 74% of patients, 21% had no change in symptoms, and 6% (3 of 65) had worsened symptoms. The 3 patients with worsened symptoms each had mild MR (1+) at 12-month follow-up. Of these 3 patients, 1 patient worsened from NYHA functional class II to class IV after experiencing chest pain requiring cardiac catheterization with angioplasty and stenting at 12 months; 1 patient increased to NYHA functional class II after a complaint of atypical chest pain, which resolved without treatment at 12 months; and the remaining patient experienced an increase to NYHA functional class II at 6 months without any reported adverse events. This patient remained at NYHA functional class II at 12 months. In patients continuing with a clip implant at 12 months with matched data, the septal-lateral annular diameter was stable. The mean annular septal-lateral dimension in systole and diastole was 3.3 ± 0.4 cm and 3.8 ± 0.4 cm at baseline and 3.4 ± 0.4 cm and 3.9 ± 0.4 cm at 12 months ($p = 0.76$ and $p = 0.21$, $n = 35$), respectively.

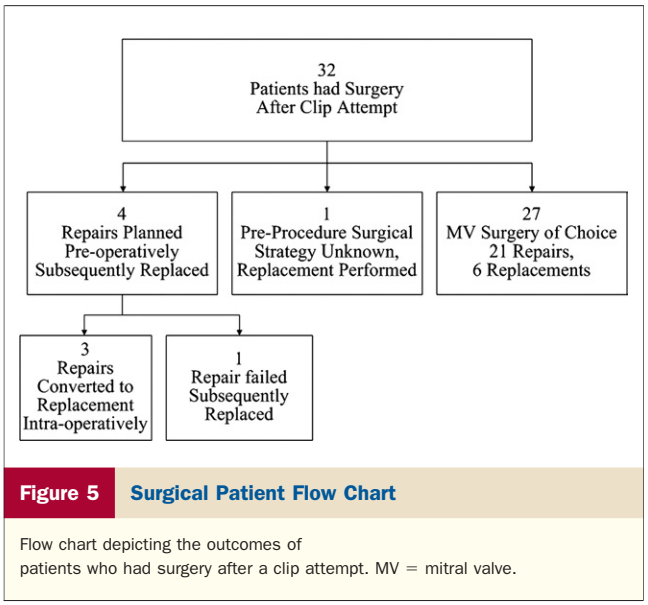

Figure 5 Surgical Patient Flow Chart

Flow chart depicting the outcomes of patients who had surgery after a clip attempt. MV = mitral valve.

In the APS cohort, Kaplan-Meier freedom from death was 95.9%, 94.0%, and 90.1% at 1, 2, and 3 years, and Kaplan-Meier freedom from surgery was 88.5%, 83.2%, and 76.3% at 1, 2, and 3 years, respectively (Fig. 6). The 23 patients with functional MR had similar acute results and durability compared with the overall population. Patients with functional MR achieved 83% APS and exhibited an 80% improvement in symptoms from baseline to 12 months, with freedom from surgery of 94.1% at 3 years.

Discussion

We report the initial experience with the MitraClip system in North America. Seventy percent of this experience consists of the participating centers' first 3 procedures. The results from the initial experience in this prospective, multicenter trial indicate that percutaneous mitral repair with the use of the MitraClip device can be successfully accom-

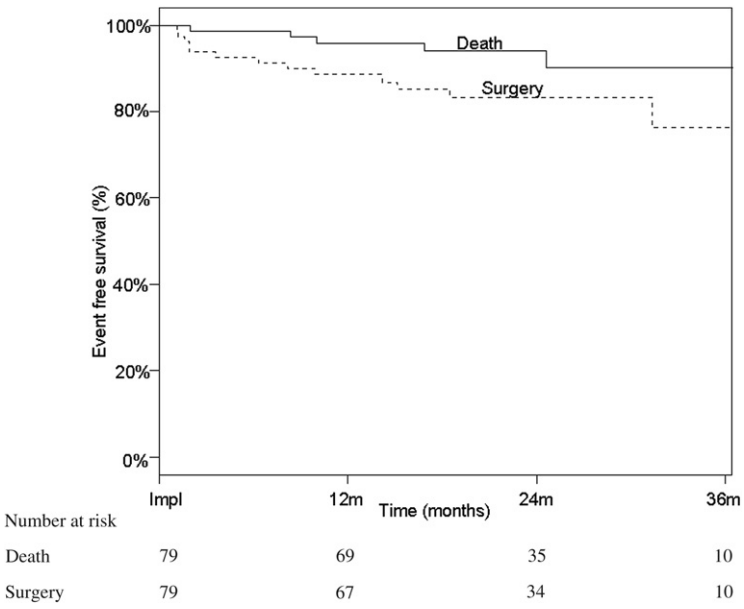

Figure 6 **Kaplan-Meier Curves for Patients With Acute Procedure Success**

Freedom from death and freedom from surgery are depicted.

plished with MR reduction to less than moderate (2+) in the majority of patients and with low mortality and morbidity. Freedom from death, need for surgery, or recurrent MR >2+ was sustained in a substantial proportion of the initial patient cohort. Furthermore, among those patients requiring MV surgery for residual or recurrent MR, surgical options were preserved, with standard repair techniques safely performed in the large majority of patients consistent with contemporaneous surgical repair rates.

The open heart surgical technique creates a double orifice by permanently coapting the MV scallops with a suture at the origin of MR. Excellent results when using this approach (without annuloplasty or leaflet resection) in selected patients with degenerative or functional MR have been reported with up to a 12-year follow-up (4). The MitraClip device is based on the surgical double orifice approach that uses a clip rather than suture to secure the mitral leaflets and is performed on the beating heart.

To ensure that a patient population in need of therapy and well suited for mitral repair with the MitraClip device was selected, the prospective use of echocardiograms was strictly used. The severity of MR and LV function requirements were used to ensure that patients had to have moderate-to-severe (3+) or severe (4+) MR. The protocol excluded patients with dilated LV (ejection fraction <25% or an LV dimension >55), coaptation length of <2 mm, and coaptation depth >11 mm in whom annuloplasty frequently has poor results.

All patients enrolled had a guideline-supported indication for mitral valve surgery. The mean MR grade at baseline was 3.3 ± 0.7. Patients in the EVEREST trial have a more severe degree of MR than patients reported in many surgical repair series, which infrequently report pre-operative MR (15–17). The median age of 71 years is 12 years older than the typical first-time isolated surgical repair patient reported in the 2007 STS database (median age of 59 years for repair and 61 years for replacement, respectively) (18).

There has been substantial learning along a steep curve. Procedure time for the first 30 procedures was a median of 241 min, whereas the final 30 procedures of this cohort were a full 1 h shorter (median time 181 min), despite almost all of the procedures representing early learning experience for individual centers. For reference, the 2007 STS database lists a median cross clamp time of 79 min, a median cardiopulmonary bypass time of 110 min, and approximately 230 min for the entire procedure ("skin to skin") for isolated MV repair in the hands of experienced cardiac surgeons (16). Efficient echocardiographic guidance is essential for this procedure, and a substantial amount of the learning can be attributed to optimizing the use of this modality (19).

One remarkable feature of the MitraClip procedure is the hemodynamic stability of patients during the procedure. Despite the fact that a device is being manipulated within the mitral orifice in a beating heart, hypotension or significant ventricular arrhythmias are rarely observed. Percutaneous mitral repair procedures have been uniformly well tolerated.

Procedural safety has been demonstrated. The complications to date are primarily related to either cardiac catheterization in general, the transseptal procedure, or to surgery

after clip treatment. The most important complication specifically related to the clip has been partial clip detachment, not clip embolization. All but 1 partial clip detachment was detected on protocol-driven echocardiograms, and none were associated with emergent or urgent surgery or precipitous clinical deterioration.

The rates of discharge from the hospital directly home are greater and hospital stay shorter than for MV surgery. Importantly, 106 (99.1%) of the 107 patients were discharged, and 104 (98%) of the 106 patients were discharged home with self-care. The 2 remaining patients (2%) who needed nursing care had surgery while hospitalized for the MitraClip procedure. This finding is in contrast to surgery, even with less-invasive surgical approaches. According to the Diagnosis Related Group handbook (20) diagnosis-related group 104 (cardiac valve and other major procedure with cardiac catheterization), 92.5% of patients are discharged, and only 40% are discharged home with self-care. For diagnosis-related group 105 (cardiac valve and other major procedure without cardiac catheterization), 95.5% of patients are discharged, and only 53.9% are discharged home with self-care.

Surgical repair was performed after procedures in which no clip was placed or when a clip was removed during surgery in the majority of patients, which is relevant because patients selected for inclusion in the EVEREST trial were not required to be repairable surgically. To 12 months, 94 (88%) of the 107 patients had a successful repair procedure (either percutaneous or surgical repair). Options for surgery were not diminished by a clip procedure because all patients requiring surgery after a clip procedure, whether they were implanted with the clip or not, were able to have mitral repair or replacement surgery (14). A large proportion (87%) of surgical procedures was performed as planned pre-operatively, and 84% of attempted surgical repairs after clip procedures were successful. This finding is comparable with the predicted repair rate reported for surgery based on pre-operative TEE (21,22). Successful surgical repair was performed as late as 18 months after a MitraClip procedure. Most surgical replacements were planned pre-operatively as the result of complex disease, advanced age, or comorbidities.

Neither the 1998 nor the 2006 ACC/AHA guidelines recommend surgery for MR severity of less than severe (graded at least 3+ or 4+ in this study). The protocol MR efficacy goal was defined as MR severity of less than or equal to moderate (2+) after clip placement. The obvious procedural goal of percutaneous mitral repair is to reduce MR as much as possible, and in this study the procedural goal was to reduce MR to mild (1+) or less with optimal placement of the MitraClip device.

Although the experience with pure functional MR is smaller, 23 patients had similar 12-month durability compared with the overall population, supporting its use regardless of whether the etiology is functional MR or degenerative MR, provided sufficient tissue is available for coaptation with the clip. It has been demonstrated in both animal and human explants that a tissue bridge forms across the clip between the leaflets (7,23,24). This healing response may help prevent future annular dilation (25). It has been hypothesized that the clip-initiated tissue bridge provides support for the clip repair (in a way partially similar to annuloplasty) and helps prevent septal-lateral dilation, as shown by the stable septal-lateral dimensions through the 12 months reported for this cohort. Preserving annular contractile function by avoiding annuloplasty may be an advantage, especially in patients with decreased LV and annular function.

The clinical application of this therapy will depend on initial MR reduction and the duration of sustained MR reduction. The recurrence of MR also has been described after successful surgical repair with linearized recurrence rates of >1+ MR of 8.3% per year and of >2+ MR of 3.7% per year (26,27). Whether the MR reduction achieved with percutaneous repair is adequate also depends on the goals of therapy. For example, an octogenarian with multiple comorbid conditions may derive clinical benefit despite suboptimal MR reduction compared with a young patient with no problem other than severe MR.

Several theoretical concepts support the potential value of this percutaneous approach for the treatment of MR. First, when MR from degenerative or functional disease results in mechanical leaflet malcoaptation, it may be amenable to the mechanical solution provided by the MitraClip device. Second, healing associated with clip results in a tissue bridge, which supports the clip repair. This tissue bridge may help support the mitral annulus, thus avoiding septal-lateral annular dilation without impairing annular contractile function. Additionally, continuity created through the tissue bridge between the annulus, the leaflets, the chordate, and the papillary muscles also may help prevent dilation of the LV. Finally, providing a method for reducing MR that avoids concomitant injury to the heart may provide an improved treatment outcome. Specifically, after open arrested heart surgery, there is abnormal LV septal motion that may affect overall LV function (28). This phenomenon has not been observed following percutaneous mitral valve repair.

This prospective, multicenter, core laboratory monitored experience with a novel first-in-class device for percutaneous MR therapy demonstrated acute reduction of MR in the majority of patients, with sustained freedom from death, need for surgery, or recurrent MR >2+ in a substantial proportion of patients after 1 year in the initial patient cohort. Annular diameter was stable through 12 months, indicating absence of further annular dilation. This cohort also experienced improved symptoms, indicating that clinical benefit was associated with the achieved MR reduction. A randomized comparison of percutaneous repair with the MitraClip device to surgical valve repair or replacement is underway, and 12-month follow-up in a 78-patient high-risk registry of patients

with an STS-predicted operative mortality of ≥12% has recently been completed.

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REFERENCES

1. Alfieri O, Maisano F, DeBonis M, et al. The edge-to-edge technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 2001;122:674–81.
2. Maisano F, Torracca L, Oppizzi M, et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. Eur J Cardiothorac Surg 1998;13:240–5.
3. Maisano F, Schreuder JJ, Oppizzi M, Fiorani B, Fino C, Alfieri O. The double orifice technique as a standardized approach to treat mitral regurgitation due to severe myxomatous disease: surgical technique. Eur J Cardiothorac Surg 2000;17:201–15.
4. Maisano F, Vigano G, Blasio A, Colombo A, Calabrese C, Alfieri O. Surgical isolated edge-to-edge mitral valve repair without annuloplasty: clinical proof of the principle for an endovascular approach. EuroInterv 2006;2:181–6.
5. Maisano F, Caldarola A, Blasio A, De Bonis M, La Canna G, Alfieri O. Midterm results of edge-to-edge mitral valve repair without annuloplasty. J Thorac Cardiovasc Surg 2003;126:1987–97.
6. Fann JI, St. Goar FG, Komtebedde J, Oz MC, Block PC, Foster E, et al. Beating heart catheter-based-edge-to-edge mitral valve procedure in a porcine model; efficacy and healing response. Circulation 2004;110:988–93.
7. St. Goar FG, James FI, Komtebedde J, et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. Circulation 2003;108:1990–3.
8. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase 1 Clinical Trial. J Am Coll Cardiol 2005;46:2134–40.
9. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practical Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32:1486–588.
10. Bonow RO, Carabello BA, Chaterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol 2006;48:e1–148.
11. Zoghbi WA, Enriquez-Sarano M, Foster E, et al, the American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
12. Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. Am J Cardiol 2007;100:1577–83.
13. Herrmann HC, Kar S, Siegal R, et al. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. EuroInter 2009;4:437–42.
14. Dang NC, Aboodi MS, Sakaguchi T, et al. Surgical revision after percutaneous mitral valve repair with a clip: initial multi-center experience. Ann Thor Surg 2007;80;2338–42.
15. Acker MA, Bolling S, Shemin R, et al, Acorn Trial Principal Investigators and Study Coordinators. Mitral valve surgery in heart failure: insights from the Acorn Clinical Trial. J Thorac Cardiovasc Surg 2006;132:568–577.e1–4.
16. Gillinov AM, Blackstone EH, Rajeswaran J, et al. Ischemic versus degenerative mitral regurgitation: does etiology affect survival? Ann Thoracic Surg 2005;80:811–819, discussion 809.
17. Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. Ann Thoracic Surg 2004;77:1598–606.
18. Society of Thoracic Surgeons. STS National Database. Mitral valve repair and replacement patients. Incidence of complications summary. 2007. Available at: http://www.sts.org/sections/stsnationaldatabase/. Accessed June 16, 2009.
19. Silvestry FE, Rodriguez LL, Herrmann HC, et al. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST I. J Am Soc Echocardiog 2007;20:1131–40.
20. Solucient, LLC. The DRG Handbook. Evanston, IL: Solucient, LLC, 2005.
21. Hellemans I, Pieper E, Ravelli A, et al. Prediction of surgical strategy in mitral valve regurgitation based on echocardiography. Am J Cardiol 1997;79:334–8.
22. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. Circulation 2007;115:881–7.
23. Privitera S, Butany J, Cusimano, RJ, Silversides C, Ross H, Leask R. Alfieri mitral valve repair: clinical outcome and pathology. Circulation 2002;106:e173–4.
24. Luk A, Butany J, Ahn E, et al. Mitral repair with the Evalve MitraClip device: histopathological findings in the porcine model. Cardiovasc Physiol 2008 Aug 12 [E-pub ahead of print].
25. De Bonis M, Lapenna E, La Canna G, et al. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy. Circulation 2005;112 Suppl I:I402–8.
26. Flameng W, Herijgers P, Bogaerts K. Recurrence of mitral valve regurgitation after mitral valve repair in degenerative valve disease. Circulation 2003;107:1609–13.
27. Flameng W, Meuris B, Herijgers P, Herregods MC. Durability of mitral valve repair in Barlow disease versus fibroelastic deficiency. J Thor Cardiovasc Surg 2008;135:274–82.
28. Ribeiro P, Nihoyannopoulos P, Farah S, et al. Role of transient ischaemia and perioperative myocardial infarction in the genesis of new septal wall motion abnormalities after coronary bypass surgery. Br Heart J 1985;54:140–4.

Key Words: mitral repair ■ percutaneous valve therapy ■ mitral regurgitation.

APPENDIX

For a complete list of the Evalve Investigators, please see the online version of this article.